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BRIEF REPORT

# Postnatal temporal changes of foetal haemoglobin in prematurely born infants

Foetal haemoglobin (HbF) is vital for adequate oxygen delivery to the developing fetus.[1] Lower HbF levels in preterm infants have been associated with increased risk of developing retinopathy of prematurity (ROP)[1] and bronchopulmonary dysplasia (BPD).[2] Despite the potential association of HbF with pathology related to prematurity, HbF levels are not routinely reviewed in everyday practice and the pattern of postnatal HbF levels has been predominately studied in term infants. HbF levels in term infants have been found to be reduced to <10% of the total haemoglobin by 16 weeks of postnatal age.[3] Following this, HbF levels in term infants continue to gradually decline to reach adult levels.[2,3] Bard studied 25 infants of 27–32 weeks of gestation in 1973 and reported that HbF exhibited a steady postnatal decline which resembled the in-utero transition.[4]

Variations in HbF levels with postnatal age have not been described in the current-era population of prematurely born infants, which includes viable infants born as early as 22 weeks of gestation. We aimed, therefore, to illustrate the course of HbF levels in prematurely born infants whilst admitted on the neonatal unit.

A retrospective, observational analysis of HbF levels of all infants born <30 weeks gestation and admitted to the tertiary neonatal intensive care unit of King's College Hospital, London, United Kingdom, from January 2019 to January 2021 was undertaken. The study was registered with the local clinical governance department. HbF levels from every blood gas analysis (ABL90 FLEX PLUS analyser, Radiometer UK Ltd), performed throughout the duration of each infant's admission, up to 150 days of life, were included. The total haemoglobin measured by the ABL90 Flex Plus has been reported to have a high correlation with the haemoglobin measured by central lab analysers.[5] Blood gas analysis formed an essential aspect of routine neonatal care, and no additional blood gas samples were performed. HbF levels are presented as a fraction (%) of total haemoglobin concentration and mean HbF levels across all infants by postnatal age were reported. According to local guidelines, preterm infants were transfused with 15 ml/kg of packed red cells when total Hb was <13.3 g/dl in mechanically ventilated infants, <10 g/dl in infants on non-invasive respiratory support and <8g/dl in convalescent infants not receiving any respiratory support. The reticulocyte count percentage was recorded on admission, at the lowest value and prior to discharge. All infants were screened for sickle cell and thalassemia according to national guidance. Transcutaneous oxygen saturation targets were 91%–95%.

A total of 4,631 blood gas samples were studied from 103 infants. The included infants had a median (range) gestational age of 27.4 (22.4–29.9) weeks [<24 weeks, $N = 9$; 24–26 weeks, $N = 24$; 26–28 weeks, $N = 31$; 28–30 weeks, $N = 39$] and a birth weight of 865(395–1,710) gr. They received a median (interquartile range, IQR) 6 (3–12) blood transfusions at 19 (6–39) days. The median (IQR) reticulocyte percentage on admission was 6.5 (4.2–10.6)%, at the lowest value 2.4(1.5–3.3)% and prior to discharge 3.5(2.8–4.4)%. None of the infants was diagnosed with sickle cell disease or thalassemia.

Median HbF levels (range) throughout the first 150 days of postnatal age were 23.5(16.0–81.5)%. The decline in mean HbF levels in prematurely born infants following birth (Day 0) is displayed in Figure 1A. Following day 60 of life, a slight increase in mean HbF levels was observed in all included infants. Differences in the postnatal HbF levels by gestational age are displayed in Figure 1B. Infants born <24 weeks displayed a steeper decline in HbF levels in the first 20 days of life and a steeper rise in HbF compared with infants born at >24 weeks gestation.

Our study reported temporal trends in postnatal HbF levels in a current cohort of preterm infants, including infants of very low gestations. Premature delivery abolishes the hypoxic stimulus required for infants to produce erythropoietin, hindering adequate postnatal erythropoiesis and contributing to the significant reduction in HbF levels observed in the first two weeks of life.[1] In addition, a reduction in HbF levels may also result from iatrogenic factors, such as repeated blood sampling and blood transfusions of Haemoglobin A (HbA)-containing blood.[2]

In our study, the steepest decline in HbF over the first two weeks of life was observed in infants born less than 24 weeks, as the most premature infants will be more vulnerable to the above factors. Reduced levels of HbF may play an important role in the development of preterm morbidity such as BPD or ROP.[1,2] Lower HbF levels, in particular, if replaced by adult HbA via transfusion, may exacerbate the oxidative pathology contributing to these conditions.[1,2]

We have highlighted important differences in the trajectory of HbF levels between those infants born less than 24 weeks gestation.

**Abbreviations:** BPD, Bronchopulmonary Dysplasia; HbA, Haemoglobin A; HbF, Foetal Haemoglobin; IQR, Interquartile Range; ROP, Retinopathy of Prematurity.

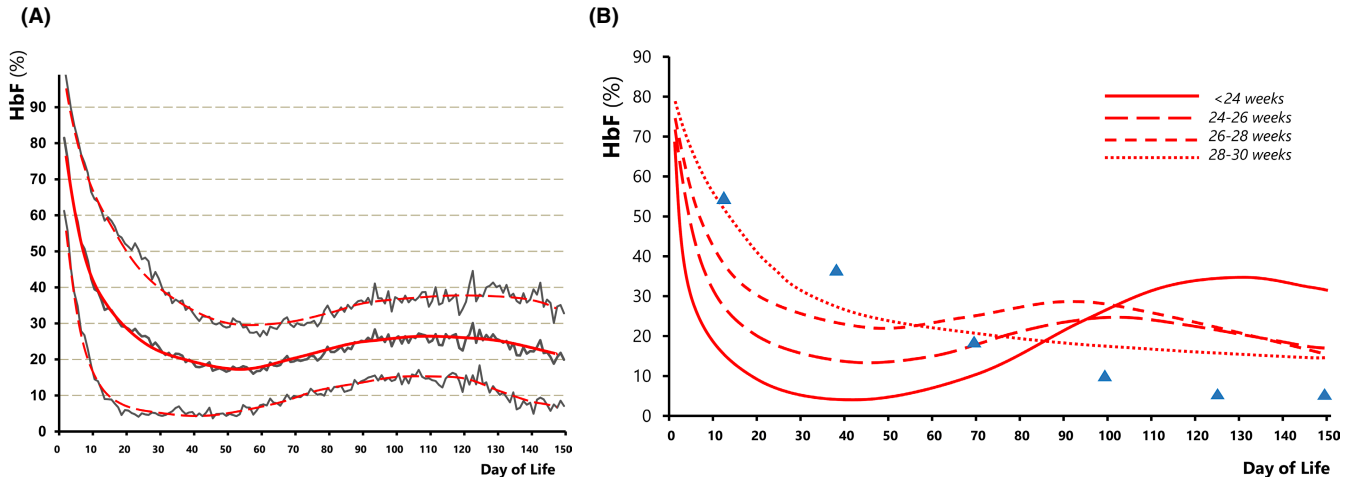


FIGURE 1 (A) Mean HbF per day +/− one standard deviation during the first 150 days of life. The actual values and smoothed superimposed lines are presented. (B) Differences in the trend of mean HbF during the first 150 days of life in different gestational age groups. Mean values of HbF in term infants are depicted as solid triangles as per Bard et al, 1975

Infants born >24 weeks gestation displayed HbF trends similar to those previously reported in term infants, although they retained a higher percentage of HbF compared with term infants.[3] In infants born before 24 weeks, however, there appears to be a persistence of higher HbF beyond that observed in infants born after this gestation. Because HbA production is believed to only commence at 30 weeks' gestation, postnatal HbF production in these infants may persist for longer following birth.[2] As such, the observed relative rise in the percentage of HbF in infants <24 weeks gestation may be due to a continued production of HbF, alongside a decreased need for blood sampling and a reduced transfusion requirement associated with greater maturation and a degree of clinical improvement. It is plausible that this phenomenon contributes to the weaning and recovery of these infants as the higher affinity of HbF with oxygen might partly explain the decreasing oxygen needs during the later recovery phase.

Given the association of lower HbF with long-term complications, future studies could evaluate whether HbF levels could potentially be incorporated in decision-making on blood transfusion thresholds or transcutaneous saturation targets.

To conclude, extremely premature infants exhibit a second peak in postnatal HbF levels which is more pronounced in those infants born below 24 weeks of gestational age.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest in relation to this study.

## AUTHOR CONTRIBUTIONS

NB collected, analysed the data and wrote the first version of the manuscript. EW collected and analysed the data. AG critically revised the manuscript and contributed to data interpretation. TD conceived the study and supervised the project. All authors were involved in revising the manuscript and approved the final version.

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